CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214793Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 129952

FDA MEETING MINUTES

Dr. Simon Ducher, PharmD
Progenics Pharmaceuticals, Inc.
One World Trade Center - 47th Floor - Suite J
New York, NY, 10007

Dear Dr. Ducher:

Please refer to the Investigational New Drug Application (IND) 129952, Meeting Package dated January 24, 2020, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [F-18] DCFPyL.

Regarding the Type B Pre-NDA meeting on February 24, 2020, please find enclosed the FDA minutes dated March 25, 2020.

Please notify us of any significant differences in understanding the meeting discussion.

If you have any questions regarding this IND, please contact me at:
Thuy.Nguyen@fda.hhs.gov or (301) 796-1427.

Sincerely,

{See appended electronic signature page}

Thuy M. Nguyen, MPH
Senior Regulatory Health Project Manager
FDA CDER - Division of Medical Imaging and Radiation Medicine (DMIRM)
U.S. Food and Drug Administration

Enclosure: **FDA Minutes**

U.S. FOOD & DRUG ADMINISTRATION

FDA MEETING MINUTES

IND: **129952**

DRUG NAME: **[F-18] DCFPyL**

SPONSOR: **Progenics Pharmaceutical, Inc.**

DATE: **February 24, 2020**

SPONSOR PARTICIPANTS:
Asha Das, MD, Chief Medical Officer
Simon Ducher, PharmD, Senior Director, Regulatory Affairs
Jouliana Jean-Paul, JD, Associate Director, Regulatory Affairs
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Key Opinion Leaders:

(b) (4)

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Jian Wang, PhD, Director, Regulatory Science
Sue-Jane Wang, PhD, Acting Deputy Director, Division of Biometrics I

I. Background:

The specific objectives and outcomes expected from the Type B Pre-NDA Face-to-Face meeting scheduled for February 24, 2020 included the following:

- Obtain agreement that the OSPREY and CONDOR efficacy and safety results support an NDA filing (b) (4)
- Obtain agreement that the Clinical Pharmacology data package supports the ^{18}F-DCFPyL NDA submission
- Obtain concurrence on the proposed Format and Content of the eCTD dossier.

Progenics received on February 20, 2020 the preliminary comments from the Agency. The Sponsor thanked the Agency for their preliminary feedback with thoughtful comments and suggestions.

To support the discussion, a slide presentation was sent to the Agency on February 24, 2020 to further address Questions 1, 2, 4, 6/8 (Slides 7-17) and the FDA Additional Comments AC1, AC3, AC2, AC5, AC7, AC8, AC10 (Slides 19-25). Progenics acknowledged and agreed with the Agency's responses for Questions 3, 5, 7, 9, 10, 11, 12, 13, 14 and the FDA Additional Comments AC4, AC6, AC9.

II. Summary of Discussion:

Progenics began by providing a summary of the ^{18}F-DCFPyL development program and indicated that an NDA is planned for early 3Q 2020.

Based on the data package, Progenics proposed the following indication: (b) (4) (b) (4)

Question 1 [Slides 7-14]

The Agency acknowledged the potential clinical utility of ^{18}F-DCFPyL in patients in OSPREY Cohort A and CONDOR studies [Slide 7]. Progenics further discussed the OSPREY Cohort B patient population and the intended clinical use in this patient setting.

Progenics presented an overview of the prostate disease landscape as it relates to the NDA submission and the current PCWG3 construct developed in part with the FDA [Slide 8]. [Slides 9- 12].

Progenics continued by illustrating how the data from OSPREY Cohort B, which included patients with metastatic disease and also non-metastatic disease based on conventional imaging, support the clinical utility of ^{18}F-DCFPyL PET imaging in the spectrum of recurrent or metastatic prostate cancer [Slide 13]. Specifically, Progenics highlighted the proportion of patients with shifts in disease stage as a result of ^{18}F-DCFPyL PET imaging [Slide 14].

The Agency inquired about pathology verification in the patients who had shifts in disease stage as presented in Slide 14. Progenics agreed that the available pathology findings for these patients will be presented in the NDA.

Question 2a [Slide 15]

Progenics agreed with the Agency's recommendation to not pool the efficacy data and stated that the OSPREY Cohort B and CONDOR efficacy data will be presented side by side in the SCE. The ISE SAP will be revised accordingly.

The Agency had no further comments.

Question 4 [Slide 16]

Progenics advised that in addition to safety data from OSPREY and CONDOR studies, a safety summary from all published clinical studies with ^{18}F-DCFPyL (including published JHU studies) will be included in the NDA, under Module 2, Section 2.7.4 "Literature review of clinical safety and toxicity profile."

The Agency agreed with this approach and asked to incorporate a summary of safety information received from the investigator-initiated trials (IITs) that are available to Progenics, similar to what has been presented in the annual report for ^{18}F-DCFPyL. Progenics confirmed that this will be provided in the NDA to the extent of the information available to Progenics from these IITs.

Questions 6/8 [Slide 17]

Progenics indicated that the renal impairment data (PK report) and the ECG data summary will be part of the OSPREY Clinical Study Report (CSR) but not as full stand-alone reports.

The Clinical Pharmacology reviewer commented that the Agency would like to have PK /renal impairment data and ECG data from OSPREY in the Clinical Pharmacology Summary (Module 2, Section 2.7.2) and also in Module 5. Progenics confirmed that the PK/renal impairment data will be provided in Module 2, Section 2.7.2 along with the hyperlink to a stand-alone PYL2301 PK report located in Module 5, Section 5.3.3.2. Regarding the ECG data, a summary will be provided within Module 2, Section 2.7.2 along with the hyperlink to the source data located in the OSPREY CSR which is located in Module 5, Section 5.3.5.2.

FDA Additional Comments AC1 [Slide 19]

Progenics presented a summary of the reasons why patients in CONDOR were not followed for efficacy/SOT assessments. To account for this missing and unevaluable data, sensitivity analyses of the primary endpoint will be submitted in the NDA, including multiple imputation and tipping point analyses as well as re-assigning unevaluable records with a central ^{18}F-DCFPyL positive finding as false positives.

The Agency requested that these unevaluable records be flagged in the dataset, and that the reason for early discontinuation be included. Progenics confirmed to include this information in the NDA.

FDA Additional Comments AC3 [Slide 20]

Progenics confirmed that patient-level PPV analyses are performed at the region and lesion level. The number and locations of all ^{18}F-DCFPyL positive lesions as well as all reference standard- assessed lesions will be included in the dataset for the NDA.

The Agency clarified that they are seeking the analyses at the specific lesion level. Progenics responded that patients could have multiple lesions and up to 64 sites of disease recorded; therefore, diagnostic performance at an individual lesion-level would not be meaningful. Progenics asked for clarification as it relates to the calculation and presentation of this data. The Agency replied that they are looking for a lesion-level PPV calculation defined as: all SOT verified ^{18}F-DCFPyL PET positive lesions (i.e. True Positive lesions) divided by all ^{18}F-DCFPyL positive SOT assessed lesions. The Agency requested the calculation be presented both for pathology only and for all SOTs.

The Agency asked if a radiologist made a determination of localization comparing the Truth Panel-verified lesions to the central PyL-reader verified lesions. Progenics indicated that lesion matching between the Truth Panel findings and the Central PyL reader findings were performed algorithmically by statistical programming based on an anatomical location code list.

The FDA asked for multiple imputation and tipping point analyses to be performed for these lesion-level endpoints (as done for the primary endpoint). Progenics clarified that due to the very small numbers for different lesion-levels, multiple imputation and tipping point may not always be feasible and/or meaningful. The Agency agreed that multiple imputation analysis would not need to be carried out but tipping point analyses should still be performed for the lesion-level calculation. Progenics agreed to carry out these analyses as long as there are enough data to perform them. Results will be included in the NDA accordingly.

FDA Additional Comments AC2 [Slide 21]

Progenics confirmed that N0 will be separated from Nx, and M0 separated from Mx, in the presentation of prior staging in the NDA. Progenics further clarified that baseline prior staging is by AJCC, which does not necessarily represent radiographic disease state at study entry but instead staging at time of initial diagnosis or subsequent pathologic verification. This was reflected by the length of time from last staging to study entry for each patient population. As such, seeking reasons for AJCC Nx and Mx will not be particularly useful to help with the interpretation of results.

In terms of baseline imaging data for both studies, Progenics clarified that for CONDOR results of all baseline imaging modalities performed for a patient's inclusion into the study will be in the NDA. For OSPREY, all patients had baseline CT/MRI and whole-body bone scans, and the central read results of these images will be provided in the NDA. Overall, this baseline imaging information will be most applicable for interpretation of study results.

The Agency indicated that this clarification addressed their question.

FDA Additional Comments AC5 [Slide 22]

Progenics described the tissue acquisition and pathology assessments in OSPREY Cohort B. Ultimately, only one biopsy and pathology assessment per patient is captured in the database. Progenics stated that the provision for two possible biopsies in the protocol was to allow for technical issues that could occur in the process and that only one biopsy was performed per patient.

The Agency indicated that this clarification addressed their question.

FDA Additional Comments AC7 [Slide 23]

For the biopsies in OSPREY Cohort B, Progenics explained that two patients' biopsies (lung and spine) were histologically positive for small cell carcinoma and interpreted as ^{18}F-DCFPyL positive. Dr. (b) (4) further described the implications of this finding in medical practice, i.e., on occasion a patient may be found to have a synchronous non-prostate malignancy detected on ^{18}F- DCFPyL PET/CT and this is valuable information to inform their treatment decisions.

The Agency inquired about the treatment for the patient with small cell carcinoma found in the lung, to which Progenics explained that the patient's post-biopsy treatment course was not captured in the database per protocol. (b) (4)

FDA Additional Comments AC8 [Slide 24]

Progenics described the potential reason as to why the lower bound of the 95% confidence interval of the PPV was less than the sample prevalence for 2 of the 3 readers in OSPREY Cohort B. Progenics specified this may be due to a very high prevalence resulting from patient inclusion criteria and targeted biopsy as well as the overall low negative patient sample. Notwithstanding, the overall PPV is consistently high (81-88%) and statistically significant across all 3 readers. This finding further indicates the importance of reader training. Progenics stated they would perform further analyses and may put forth other possible explanations.

The FDA had no further comments.

FDA Additional Comments AC10 [Slide 25]

For OSPREY Cohort A, Progenics explained that the analysis treated all colocalizations between the central readers and pathology results at the subject level where pelvic lymph node packet locations aligned. In case of a discrepancy, the determination was based on positive pathology. Progenics added that the requested 2x2 table will be presented in the NDA.

The FDA had no further comments.

In conclusion, Progenics expressed eagerness to submit this NDA for ^{18}F-DCFPyL and make the drug available to patients as expeditiously as possible.

FDA REGULATORY COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that the FDA Chemistry WRO responses will be issued to you by April 3, 2020.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Refer to the draft Guidance for Industry: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft Guidance for Industry: *Applications Covered by Section 505(b)(2)* (October 1999).[3] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[4]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a Sponsor relies.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.regulations.gov

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)).

If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*

(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry: *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry: *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

SUBMISSION FORMAT REQUIREMENTS

All submissions should be submitted with a cover letter and applicable FDA Forms.

The Electronic Common Technical Document (eCTD) is CDER and CBER standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File and Commercial: Pre-INDs, INDs and Exploratory INDs **must be** submitted in eCTD format.

[5] https://www.fda.gov/media/85061/download

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. For additional information, see FDA.gov.[6]

SECURE EMAIL

Secure Email is required for all email communications from the FDA to the Sponsors and / or Sponsor's Authorized Representatives when confidential information is included in the message.

Sponsors and Sponsor's Authorized Representatives must each establish a Secure Email account with the FDA to receive email communications from the FDA that include confidential information (e.g., information requests (IRs), meeting responses, courtesy copies of FDA letters, labeling revisions, trade secrets, manufacturing, or patient information, etc).

To establish a Secure Email with the FDA, send an email request: SecureEmail@fda.hhs.gov.

Note: A secure email may not be used for formal official regulatory submissions.

[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

ATTACHMENT: Sponsor Meeting Slide Presentation – February 24, 2020

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THUY M NGUYEN
03/25/2020 04:00:04 PM

IND 129952

FDA MEETING MINUTES

Dr. Simon Ducher, PharmD
Progenics Pharmaceuticals, Inc.
One World Trade Center - 47th Floor - Suite J
New York, NY, 10007

Dear Dr. Ducher:

Please refer to the Investigational New Drug Application (IND) 129952, Meeting Package dated March 26, 2019, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [F-18] DCFPyL.

Regarding the Type B EOP meeting on May 15, 2019, please find enclosed the FDA minutes dated June 14, 2019.

Please notify us of any significant differences in understanding the meeting discussion.

If you have any questions regarding this IND, please contact me at: Thuy.Nguyen@fda.hhs.gov or (301) 796-1427.

Sincerely,

{See appended electronic signature page}

Thuy M. Nguyen, MPH
Senior Regulatory Health Project Manager
FDA CDER - Division of Medical Imaging Products
U.S. Food and Drug Administration

Enclosure: **FDA Minutes**

FDA MEETING MINUTES

IND: **129952**

DRUG NAME: **[F-18] DCFPyL**

SPONSOR: **Progenics Pharmaceutical, Inc.**

DATE: **May 15, 2019**

SPONSOR PARTICIPANTS:
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Asha Das, MD, Chief Medical Officer
Simon Ducher, PharmD, Senior Director, Regulatory Affairs Clinical
Jessica Jensen, MPH, Senior Vice President, Clinical Development
Tess Lin, PharmD, Associate Director, Clinical Development
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Yakov Rotshteyn, PhD, Distinguished Director, Product Development
Nancy Stambler, DrPH, Executive Director, Biometrics
Vivien Wong, PhD, Executive Vice President, Development
Key Opinion Leaders

(b) (4)

FDA PARTICIPANTS:
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Jonathan Cohen, PhD, Pharm/Tox Reviewer
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Alex Gorovets, MD, Clinical Secondary Reviewer & Division Deputy Director
Sam Habet, PhD, Clinical Pharmacology Reviewer
Alex Hofling, MD, PhD, Clinical Primary Reviewer
Christy John, PhD, Clinical Pharmacology Team Leader
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Lou Marzella, MD, PhD, Division Director
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Thuy M. Nguyen, MPH, Senior Regulatory Health Project Manager
Sue-Jane Wang, PhD, Acting Deputy Director, Division of Biometrics I
Jyoti Zalkikar, PhD, Statistical Secondary Reviewer

AGENDA: Regarding IND 129952: Meeting Package dated March 26, 2019, to discuss the FDA Meeting Responses of May 10 (Attachment #1) and the Sponsor slides received on May 14, 2019 (Attachment #2).

Background:

The specific objectives and outcomes expected from the Type B (EOP) Face-to-Face Meeting scheduled for May 15, 2019 included the following:

- To obtain the Agency's perspective and agreement on the results from the OSPREY study, consisting of the proposed sub-analysis as an acceptable presentation of the OSPREY Cohort A data to support the proposed indication in the planned NDA submission (Question 1).
- Obtain concurrence with the Agency on the sufficiency of the following eCTD dossier components to support an NDA submission of ^{18}F-DCFPyL for the proposed indication:
    - Two pivotal studies (OSPREY and CONDOR) (Questions 2-3)
    - Clinical pharmacology studies (Questions 4-5)
    - Nonclinical package (Question 6)
    - CMC package (Questions 7-12)
    - General/Regulatory (Questions 13-14)

To support the discussion, a slide presentation was sent to the Agency on May 14, 2019 to further address Questions 1a, 2, 3a, 3b, 4, and 9. Progenics acknowledged and agreed with the Agency's responses for Questions 1b, 5, 6, 7, 8, 10, 11, 12, 13 and 14 and had no additional comments.

As advised by the Agency, the order of the questions discussed at the meeting was Clinical Pharmacology (Q.4) followed by CMC (Q.9), and finally Clinical and Statistical (Qs. 1a, 2, 3a, and 3b).

Summary of Discussion:

Progenics began by providing a summary of the ^{18}F-DCFPyL development program,

The indication being proposed is: (b) (4) [redacted]

The Sponsor also provided a summary of the current status of the PyL development program and indicated that an NDA will be submitted as quickly as possible following the completion of the Phase 3 CONDOR study, and no later than 4Q 2020 [Slide 5].

Question 4 [Slide 33]

Progenics stated that kidney function was assessed for all patients in OSPREY and, as recommended by the Agency, subgroup analyses of effect of renal function on efficacy of ^{18}F-DCFPyL (sensitivity and specificity) will be conducted with the results to be included in the planned NDA submission.

The Agency confirmed that this was acceptable.

Question 9 [Slide 34]

(b) (4)

The Agency acknowledged the clarification and advised that it would be key to provide the method validation package for the DSP and characterization of the DSP reference standards used for the chiral assay in the NDA. Progenics confirmed this information will be provided.

Question 1a

[Slide 7] Progenics underscored that the PyL clinical development program has been established to capture diagnostic performance data across the spectrum of initial treatment, recurrent and metastatic prostate cancer. In total, this will include nearly 600 subjects imaged with over 400 verified against histopathology as a truth standard.

In OSPREY, the patients that entered cohort A met criteria of high- or very-high-risk disease by NCCN guidelines. Hence, these are patients planned for initial localized therapy based on the absence of known regional nodal (N1) or distant (M1) metastatic disease. This is deemed important because patients with known N1 or M1 disease should be treated under a different paradigm, specifically systemic therapy.

[Slide 9] Progenics summarized the significant unmet diagnostic need to properly stage high risk patients for therapy planning due to the low performance characteristics (i.e. PPV and NPV) of current standard of care imaging, specifically bone scan, pelvic CT and MRI.

[Slide 11] Progenics presented the pre-study staging data for patients that entered cohort A of the OSPREY study in which nearly all patients had no known regional or distant metastatic finding based on standard of care imaging. Due to this baseline disposition, nearly all N1or M1 metastatic finding in the study population is deemed new information the patient otherwise did not have prior to PyL imaging.

Dr. Hofling asked how NX could be interpreted. Progenics indicated this likely represents the unreliability of current imaging modalities to permit clinicians to confidently diagnose nodal disease.

Additional information was then provided in the Slides 13-27 to address the 4 items specifically requested by the Agency under Question 1a regarding the OPSREY trial methodology and results.

Question 1a: Progenics response to additional information requested

1. *The method by which regional lymph node data was used to generate patient-level results*

[Slides 13-14] Progenics reviewed the methodology of pelvic lymph node tissue acquisition to evaluate the diagnostic performance of PyL in this setting.,

Dr. (b) (4) a surgeon who performed several surgeries in the OSPREY study further described the tissue acquisition methodology and challenges in verification of this tissue sample against a pathologist's review. Dr. (b) (4) commented that all men underwent radical prostatectomy and pelvic lymph node dissection because of underlying risk for micrometastatic disease.

Of the anatomic locations (i.e. pelvic right, pelvic left, pre-sacral, or other), the FDA asked how often tissue from the pre-sacral lymphadenectomy template was collected. Dr (b) (4) explained that while the right and left pelvic packets should always be included, presacral collection was less common.

Progenics then clarified that correspondence of the anatomic location on PyL imaging and pathology was not required for success. Dr. Marzella asked if the surgeon may change their surgical template based on findings from the scan. Dr. (b) (4) affirmed that he would be more interested in cancelling the surgery

The FDA emphasized the importance of colocalization to evaluate diagnostic performance and requested this analysis in the planned NDA submission. Progenics agreed to include these results in the OSPREY Clinical Study Report.

2. *Analysis of inter-reader and intra-reader agreement.*

[Slide 15] Progenics presented the results of inter-reader and intra-reader agreement reflecting strong reader performance.

3. *Discussion of the impact that the diagnostic performance characteristics of ^{18}FDCFPyL PET might have on its anticipated clinical utility in the pre-prostatectomy population.*

[Slide 16] Progenics reviewed the performance of PyL to detect pelvic lymph node metastases.

Notably, 28 subjects in this preoperative population would have been upstaged to M1 disease based on the finding of distant metastatic disease by at least one PyL reader.

Dr. Hofling inquired about any follow-up conducted for the aforementioned 28 subjects. Progenics replied that data from one biopsy of a metastatic finding was collected in the database and confirmed to be true positive.

[Slide 17] Progenics underscored the clinical relevance of the findings in OSPREY Cohort A and the potential of PyL to fill a current unmet medical need, specifically in the staging of patients with high risk disease.

[Slide 18] Because of the lower than expected sensitivity, further analysis was conducted by Progenics taking into account resolution limits of PET scanners.

When the analysis was restricted to subjects with pelvic lymph node metastatic deposits >5 mm, there was an improvement in sensitivity.

In response to a question from Dr. Ganley regarding the detection limits of FDG PET, Dr. (b) (4) explained that with FDG PET and other PET tracers, such limits are generally known limitations and the general scanner resolution is 5 to 7 mm. The relationship when looking at multiple lymph nodes and tumor deposit volume is likely to be on a continuum. In OSPREY and CONDOR, positive lesions are defined as focally increased PyL uptake compared to background (no SUV was used). As with other oncology PET tracers, this is a visual interpretation, i.e. if an image is difficult to interpret, then the scan will be called 'indeterminate' and clinicians will aim to find out more information using other available means.

Dr. Marzella asked about any findings outside the pelvis (how common they were and how often these patients were followed). Progenics advised that central reader results were not reported back to the clinical sites, so any findings may or may not have been acted upon. Dr. Marzella further asked if Progenics had any data on local reads. Progenics clarified that local read results were not captured in OSPREY but are being collected in CONDOR.

Dr. (b) (4) illustrated the clinical utility with two patient cases from Cohort A (b) (4) [Slides 21-25]. He emphasized the risks of prostatectomy, including incontinence and impotence. He stated that false negatives are clinically less relevant than false positive. Dr. (b) (4) asserted that patients have a real need for PSMA imaging modalities and only those with sufficient resources are currently able to obtain access at institutions such as (b) (4)

The FDA commented that they understand the clinical utility of PyL in the preoperative setting as stated by Dr. (b) (4) but questioned the potential implications (b) (4) of PyL on the drug label. These may include:

(b) (4)

Dr. (b) (4) suggested that an option for the drug label could be (b) (4) Dr. (b) (4) added that (b) (4)

[Slides 27] (b) (4)

(b) (4)

Question 2:

Progenics response to additional information requested by the FDA:

1. *Explanation for only 93 patients being evaluable out of 117 who were enrolled.*

2. *Confirmation that the 93 evaluable patients were biopsied but not always positive for cancer on histopathology.*

Progenics confirmed that for Cohort B in OSPREY, 93 patients were evaluable out of the 117 subjects who were enrolled and provided the reasons patients were deemed non-evaluable.

Of the 93 evaluable subjects evaluated, there were 22 subjects with biopsies that were negative for prostate cancer on pathology. Progenics attributed this to technical challenges of biopsy in men with metastatic prostate cancer [see details in Slide 29].

Dr. Hofling inquired if the negative cases were mostly bone lesions. Progenics advised that this information was not readily available but would be included in the NDA submission.

3. *Method by which only a single lesion was chosen for analysis in patients who had multiple biopsies.*

Progenics explained that the site submitted only one lesion for pathology for the purposes of the OSPREY trial [Slide 30]. Dr. (b) (4) added that there are inherent risks to using biopsy to confirm diagnosis. Bone is hard to biopsy, so typically nodes, liver, and lung tissues are prioritized to be biopsied.

4. *Analysis of inter-reader and intra-reader agreement.*

For Cohort B, Progenics summarized inter-reader agreement results of an overall Kappa of 0.51 with a concordance of 84% and indicated intra-reader agreement was not assessed [Slide 30].

Dr. Hofling questioned why the Kappa was lower in Cohort B vs. Cohort A. Dr. (b) (4) suggested the lower number in Cohort B may be due to the fact that PyL scans were read without a targeted anatomic location/field of view.

Question 3b [Slide 31]

Progenics confirmed that in addition to results from CONDOR and OSPREY studies, there is a plan to supplement a future NDA submission with well-controlled clinical studies using PyL from published literature. However, primary datasets from these studies are not expected to be available for NDA review as they are not sponsored-studies and differ in terms of standards.

The FDA commented that this approach was acceptable.

Question 3a [Slide 32]

Progenics clarified that urinalysis was performed only post-PyL administration in the PK subgroup of the OSPREY study and analyzed solely for radioactivity concentration and metabolic profile (clinical lab parameters were not measured). Based on data from the OSPREY study, changes in clinical lab parameters following PyL administration are very unlikely, therefore clinical urinalysis assessment was not performed.

The FDA commented that while a urinary safety finding may be unlikely, urinalysis is generally part of the safety assessment of a new drug. Dr. Hofling recommended collecting urinalysis data, including microscopic analyses, in approximately 10 patients in the CONDOR study. The Sponsor indicated that enrollment of the ongoing CONDOR study is near completion and an amendment to the study protocol would result in a delay in an NDA submission. Dr. Marzella further suggested a potential alternative where this data could be collected, pre-dose and ~24 hours post dose, as part of an Expanded Access Program of the CONDOR study. The Sponsor agreed to consider all potential options that would satisfy the requirement to support the planned NDA.

Additional Comments

Upon conclusion of the Sponsor's presentation, Dr. Marzella expressed interest in the information available for the 14 patients in OSPREY who had a change of management and did not undergo the originally planned surgery. This is considered an important finding and the FDA recommended developing a plan to present and verify the lesion finding data, which would add value to the totality of evidence in a future NDA submission. Progenics explained that OSPREY was not designed to study change of management or clinical outcomes and in fact this was not encouraged in the trial. Further, the trial is now closed and the database is locked; therefore, collecting this data would not be feasible within the clinical database. Notwithstanding, Progenics proposed to prepare individual narratives for these 14 patients (including any further anecdotal information that may be obtained from study investigators). This was considered acceptable by the Agency.

FDA POST-MEETING NOTES

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft Guidance for Industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the Guidance for Industry: *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the Phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the Pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a Phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C Meeting Request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

COMPOUNDED DRUG PRODUCT REQUIREMENTS

As described at 21 CFR 210.2(c), a drug product, including a compounded product, intended for use in a clinical study must be prepared in accordance with the current good manufacturing practice requirements appropriate for the product. For questions or clarification, contact Compounding@fda.hhs.gov.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry: *Assessment of Abuse Potential of Drugs*.[12]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry: *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe

[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf
[12] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

location or provide a link to the requested information.

Please refer to the draft Guidance for Industry: *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical*

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA Guidance for Industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new Phase 2 or Phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to

endpoint measures, dose, and/or population)

- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[13]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[14]

[13] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm
[14] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm

SUBMISSION FORMAT REQUIREMENTS

All submissions should contain a cover letter and FDA Forms 356h, 1571, 1572 and 3674 (as applicable).

The Electronic Common Technical Document (eCTD) is CDER and CBER standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File, Commercial: Pre-INDs, INDs and Exploratory INDs **must be** submitted in eCTD format.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. For additional information, see FDA.gov.[15]

SECURE EMAIL

Secure Email is required for all email communications from the FDA to the Sponsors and / or Sponsor Authorized Representatives when confidential information is included in the message.

Sponsors and Sponsor's Authorized Representatives must each establish a Secure Email account with the FDA to receive email communications from the FDA that include confidential information (e.g., information requests (IRs), meeting responses, courtesy copies of FDA letters, labeling revisions, trade secrets, manufacturing, or patient information, etc).

If needed, to establish a Secure Email with the FDA, send an email request to: SecureEmail@fda.hhs.gov.

Note: A secure email may not be used for formal official regulatory submissions

[15] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

IND 129952 / [F-18] DCFPyL

ATTACHMENT #1: FDA Meeting Responses – May 10, 2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129952

PRELIMINARY MEETING RESPONSES

Dr. Simon Ducher, PharmD
Progenics Pharmaceuticals, Inc.
One World Trade Center, 47th Floor - Suite J
New York, NY 10007

Dear Dr. Ducher:

Regarding **IND 129952 / [F-18] DCFPyL**, Type B Meeting Package dated March 26, 2019, please find enclosed the FDA Preliminary Meeting Responses – May 10, 2019.

By 12:00 pm, US ET – Tuesday, May 14, 2019, please let me via email which specific meeting questions / responses Progenics would like to discuss at the Face-to-Face meeting on May 15, 2019 at 11:30 am – 1:00 pm, US ET.

And provide any Sponsor materials (i.e., slides) for the meeting and follow-up as a formal official submission to the FDA.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at the meeting. The official record of the meeting will be the FDA-generated minutes.

If you have any questions, regarding this IND, please contact me at:
Thuy.Nguyen@fda.hhs.gov or (301) 796-1427.

Sincerely,

{See appended electronic signature page}

Thuy M. Nguyen, M.P.H.
Senior Regulatory Health Project Manager
U.S. FDA CDER - Division of Medical Imaging Products

Enclosure: FDA Preliminary Meeting Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA PRELIMINARY MEETING RESPONSES

Regarding IND 129952 / [F-18] DCFPyL, Type B Meeting Package dated March 26, 2019, below are the FDA Preliminary Meeting Responses – May 10, 2019.

These have not been fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the meeting. The FDA minutes will reflect agreements and discussion and might not be consistent with these preliminary meeting responses / comments.

SPONSOR MEETING QUESTION #1a – Clinical / Statistical

Does the Agency agree that including in the statistical analysis (b) (4) *is an appropriate presentation of the OSPREY Cohort A data for our planned NDA submission?*

FDA RESPONSE #1a

We have concerns with your proposed (b) (4) **would be a review issue.**

The following additional information regarding OSPREY Cohort A would be useful:

- **The method by which regional lymph node data was used to generate patient-level results.**
- **Analysis of inter-reader and intra-reader agreement.**
- (b) (4)
-

SPONSOR MEETING QUESTION #1b – Clinical / Statistical

Does the Agency agree that, collectively, all data from OSPREY Cohort A is sufficient to support the use of 18F-DCFPyL (b) (4) *?*

FDA RESPONSE #1b

See FDA Response #1a.

SPONSOR MEETING QUESTION #2 – Clinical / Statistical

Does the Agency agree that the totality of data from PyL2301 (OSPREY) Cohort B, and assuming positive data from the ongoing PyL3301 (CONDOR) study, is sufficient to support the use of 18F-DCFPyL (b) (4) *?*

FDA RESPONSE #2

(b) (4)

The following additional information regarding OSPREY Cohort B would be useful:

- **Explanation for only 93 patients being evaluable out of 117 who were enrolled.**
- **Confirmation that the 93 evaluable patients were biopsied but not always positive for cancer on histopathology.**
- **Method by which only a single lesion was chosen for analysis in patients who had multiple biopsies.**
- **Analysis of inter-reader and intra-reader agreement.**

SPONSOR MEETING QUESTION #3a – Clinical / Statistical

Does the Agency agree that the safety data from the OSPREY and CONDOR studies, a total of approximately 585 patients with 18F-DCFPyL Injection exposures, will provide an adequate safety database to support a future NDA submission for the proposed indication?

FDA RESPONSE #3a

The proposed size of your safety population appears generally adequate for NDA submission. We recommend that submitted safety evaluation include urinalysis performed before and after ^{18}F-DCFPyL administration in a small group of subjects.

SPONSOR MEETING QUESTION #3b – Clinical / Statistical

Does the Agency agree that the totality of data available from 2 prospective, well-controlled studies with diagnostic performance 18F-DCFPyL PET/CT evaluated against histopathology and/or a composite truth standard previously endorsed by the Division (OSPREY and CONDOR), as described in the Meeting Briefing Package, will provide sufficient efficacy data to support a future NDA submission for the proposed indication?

FDA RESPONSE #3b

If the CONDOR study meets its endpoints, additional results from the OSPREY study and other published clinical studies using ^{18}F-DCFPyL might support NDA submission. In regards to the published literature, well-controlled studies might be of particular value, especially if their primary datasets were available for review. Details regarding any approved indications would be subject to complete NDA review.

SPONSOR MEETING QUESTION #4 – Clinical Pharmacology (PK)

Based on the totality of evidence from pharmacokinetic (PK) evaluations of the PK subcohort in the OSPREY study described in the Meeting Briefing Package, does the Agency agree that the elimination pathway of 18F-DCFPyL is adequately addressed and no additional PK/ADME studies, including no special population studies, are required?

FDA RESPONSE #4

We agree that no additional PK/ADME studies are needed including special population. However, it is not clear if the degree of renal impairment (mild, moderate and severe) has any impact on the efficacy of the drug. Provide a subgroup analysis of renal function (normal, mild and moderate) vs. sensitivity and specificity in an eventual NDA submission. These results may warrant dose adjustments in specific populations, if needed.

SPONSOR MEETING QUESTION #5 – Clinical Pharmacology (PK)

Does the Agency concur that no additional drug interactions studies are required to support a future NDA of 18F-DCFPyL for the proposed indication?

FDA RESPONSE #5

We concur that no additional drug interaction studies are required to support an eventual NDA. Provide amounts and identity of metabolites (if known) in one patient in NDA submission.

SPONSOR MEETING QUESTION #6 – Nonclinical (Pharmacology/Toxicology)
Does the Agency agree that the nonclinical package for 18F-DCFPyL can be considered complete, and no additional studies are required, to support a future NDA submission?

FDA RESPONSE #6
Yes, we agree in principle that no additional nonclinical studies are required, provided that the right of reference to nonclinical study data (extended, single-dose toxicity study in rats) is obtained.

SPONSOR MEETING QUESTION #7 – Chemistry
Does the Agency agree with the proposed drug substance precursor specifications?

FDA RESPONSE #7
The specifications for the (b) (4) (drug substance precursor, DSP) appear reasonable. However, the final determination of adequacy will be a review issue.

The Division of Microbiology Assessment agrees with proposed drug substance specifications.

SPONSOR MEETING QUESTION #8 – Chemistry
Does the Agency agree with the proposed approach to establish comparability between the clinical and commercial batches of the DSP?

FDA RESPONSE #8
The approach to establish comparability of the DSP manufactured at the two facilities appears reasonable. However, side by side comparison of the product release specifications data from the facilities should be provided including the chiral purity data in the NDA for review.

SPONSOR MEETING QUESTION #9 – Chemistry
Does the Agency agree with the proposed approach to establish the specification for chiral purity?

FDA RESPONSE #9
The proposed approach to determine the chiral purity of the DSP and eventually the drug product appears reasonable. Nonetheless, neither the method for chiral analysis nor data are provided in the Meeting Package to enable the FDA to make any determination. In an eventual NDA application, provide detailed manufacturing, characterization and all relevant data of the reference standards used for the chiral assay. Provide detailed description and validation information of the analytical method used.

SPONSOR MEETING QUESTION #10 – Chemistry
Does the Agency agree with the proposed drug product specifications?

FDA RESPONSE #10
Yes, the specifications for the drug product appear reasonable. However, adequacy will be a review issue.

The Division of Microbiology Assessment agrees with the proposed drug product specifications.

SPONSOR MEETING QUESTION #11 – Chemistry
Does the Agency agree that comparability between the drug product manufactured by the optimized process and the drug product used in clinical trials can be demonstrated by compliance to the same specifications?

FDA RESPONSE #11
The approach to optimize the manufacturing process and the drug product seems reasonable. However, data for at least three consecutive drug product batches manufactured utilizing the optimized process should be provided for all the manufacturing sites. Adequacy of the data provided will be a review issue.

SPONSOR MEETING QUESTION #12 – Chemistry
Does the Agency agree that (b) (4) *from the final drug product in the three validation batches?*

FDA RESPONSE #12
(b) (4) **is unacceptable at this time. A determination will be made based on review of the data to be provided in support of the proposal in the NDA application.**
The Sponsor is referred to the following documents for additional information:
(21 CFR 212- Current Good Manufacturing Practice for Positron Emission Tomography Drugs).
We also remind the Sponsor that for a multicenter trial the FDA expects the drug product used at these sites to be the same.

SPONSOR MEETING QUESTION #13 – Nonclinical (P/T) / Regulatory
Does the Agency agree with the requested product specific full waiver of conducting developmental and reproductive toxicology studies?

FDA RESPONSE #13

Yes, we agree.

SPONSOR MEETING QUESTION #14 – Clinical / Regulatory
Does the Agency agree with the requested product specific full waiver of conducting pediatric studies?

FDA RESPONSE #14
Yes, we conceptually agree. However, you should make a separate formal iPSP submission to your IND.

FDA REGULATORY COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft Guidance for Industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the Guidance for Industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND Sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND Sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data

[1] When final, this Guidance will represent the FDA current thinking on this topic. For the most recent version of a Guidance, check the FDA Guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND Sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

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[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry *Assessment of Abuse Potential of Drugs*.[12]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA Guidance for Industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new Phase 2 or Phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

[12] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

Note: All amended / revised protocols, consent forms and any other revised documents should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on

these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[13]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid[14]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. **The following submission types:** NDA, ANDA, BLA, Master File (except Type III), Commercial: Pre-INDs, INDs and Exploratory INDs **must be** submitted in eCTD format.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, see: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see: http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

SECURE EMAIL COMMUNICATIONS

Secure Email is required for all email communications from the FDA to the Sponsors and / or Sponsor's Authorized Representatives when confidential information is included in the message.

Sponsors and Sponsor's Authorized Representatives must each establish a Secure Email account with the FDA to receive email communications from the FDA that include confidential information (e.g., information requests (IRs), meeting responses, courtesy copies of FDA letters, labeling revisions, trade secrets, manufacturing, or patient information, etc).

To establish a Secure Email with the FDA, send an email request to: SecureEmail@fda.hhs.gov

Note: A Secure Email may not be used for formal official regulatory submissions.

[13] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm
[14] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

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ATTACHMENT #2: Sponsor Slides received - May 14, 2019

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